Beyond Phenotype: The Promise of hiPSC-Based Studies of Schizophrenia.

Journal: Stem Cells

Publication Year: 2011

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PubMed link: 22009633

Funding Grants: Development of Induced Pluripotent Stem Cells for Modeling Human Disease, Training in the Biology of Human Embryonic Stem Cells and Emerging Technologies II

Public Summary:
Schizophrenia has a huge genetic component, but the exact genes responsible remain unknown. Previous imaging, drug and post-mortem studies have observed decreased brain volume, aberrant neurotransmitter signaling, reduced neuron size, and impaired myelination in SCZD. The discovery of human induced pluripotent stem cells (hiPSCs) makes it possible to study SCZD using live human neurons, even without knowledge of the genes interacting to produce the disease state. SCZD hiPSC neurons show cellular defects comparable to those identified in post-mortem human and mouse studies, and gene expression changes are consistent with predictions made by genetic studies. SCZD hiPSC neurons represent a new tool to dissect the genetic causes of SCZD.

Scientific Abstract:
Schizophrenia (SCZD) is a heritable developmental disorder. While the molecular mechanism of disease remains unclear, insights into the disorder have been made through a vast array of experimental techniques. Together, MRI brain imaging, pharmacological and postmortem pathological studies have observed decreased brain volume, aberrant neurotransmitter signaling, reduced dendritic arborization and impaired myelination in SCZD. Genome wide association studies have identified common variants as well as rare copy number variants that contribute to SCZD, while mouse models of candidate SCZD genes show behavioral abnormalities and anatomical perturbations consistent with human disease. The advent of human induced pluripotent stem cells (hiPSCs) makes it possible to study SCZD using live human neurons with a genetic predisposition towards SCZD, even without knowledge of the genes interacting to produce the disease state. SCZD hiPSC neurons show cellular defects comparable to those identified in postmortem human and mouse studies, and gene expression changes consistent with predictions made by GWAS. SCZD hiPSC neurons represent a new tool to look beyond phenotype and begin to dissect the molecular mechanisms of SCZD.